REMARKS

STATUS OF THE CLAIMS

Claims 2-12 were pending in this application. Claims 2, 3, and 4 have been amended. Following entry of the amendments claims 2-12 will be pending and at issue.

SUPPORT FOR AMENDMENTS TO THE CLAIMS

The claims have been amended to more clearly recite the claimed method. Support for the amendments can be found throughout the specification as filed and as described below.

Support for "inputting the set of gene expression data" can be found at, e.g., page 12, lines 26-28.

Support for "identifying a first subset of low-level observed intensity measurements, wherein said subset of low level observed intensity measurements have values less than an observed intensity measurement cutoff determined by a thresholding algorithm" can be found at, e.g., page 2, lines 26-29;

Support for "estimating a standard deviation, σ_ε of an additive error component, ε of the set of gene expression data using either at least one negative control or using the first subset of low level observed intensity measurements;" can be found at, e.g., page 2, line 29 through page 3, line 2; also page 5, lines 11-12.

Support for "estimating a mean background intensity measurement, α, using either at least one negative control or using the first subset of low level observed intensity measurements;" can be found at, e.g., page 2, line 22 and lines 29 to page 3, line 2; also page 6, lines 3-5.

Support for "identifying a second subset of replicated high-level observed intensity measurements from the set of gene expression data, wherein the second subset comprises several highest intensity measurements of the set or the variance of logarithms of the second subset is approximately constant;" can be found at, e.g., page 6, lines 8-17.

Support for "estimating a standard deviation, σ_η, of a proportional error component, η, of the set of gene expression data using the standard deviation of the logarithm of the second subset of replicated high-level observed intensity measurements" can be found at, e.g., page 6, lines 6-8 and lines 18-26.

Support for "using estimates of $\sigma\varepsilon$ and $\sigma\eta$ and α for estimating a variance of the observed intensity measurement, y," can be found at, e.g., page 4, line 28.

Support for "wherein μ is an expression level of a biological molecule in arbitrary units" can be found at, e.g., page 2, lines 21 and 22; also page 4, line 28.

Support for "$n_k = n_{k-1}$" can be found at, e.g., page 11, lines 16-18.

The amendments to the claims therefore add no new matter and entry is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 101: SUBJECT MATTER

Claims 2-12 were rejected under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. The Examiner stated that the claimed method "recite a series of mathematical steps ... does not recite any physical method step or transformation of data ..." and that "none of the claims actually recites any particular result ... no result is generated or output in a concrete and tangible form such that is could be comprehended and thus be useful to one performing the method."

Applicant's invention is a method for estimating the precision of gene expression data by calculating a variance utilizing estimates of various error parameters. Data (observed intensity measurements) from gene expression array experiments is used as input and are transformed into a variance that is useful for determining whether or not the data are precise, e.g., accurate, and useful for calculating relative expression levels, e.g., μ.

Without agreeing with the Examiner's opinion but rather to further prosecution, Applicant has amended claim 2 to more clearly recite the method steps, and has included a physical method step of "inputting the set of gene expression data." Therefore, the claimed method does include a transformation of data (observed intensity measurements)

and the claims recite a physical method step (inputting); a particular result (calculation of a variance) that can be comprehended and is therefore useful (e.g., for estimating precision of the data). Accordingly, Applicant believes that the claims are directed to statutory subject matter. Withdrawal of the rejection is requested.

REJECTIONS UNDER 35 U.S.C. § 101: UTILITY

Claims 2-12 were also rejected as allegedly lacking utility. The Examiner stated that "The specification does not set forth a specific and substantial utility for estimating the variance (changes) in measurements taken from a gene expression microarray, and no well established utility is provided for such a method in the prior art." Applicant respectfully disagrees.

First, the specification clearly sets out a specific and substantial utility for estimating the variance in measurement taken from a gene expression array. For example, the following quotes can be found in the specification:

> The present invention addresses the need for improved methods for analysis of microarray-derived gene expression data by providing methods for determining the precision of such data over the full range of observed expression levels. (page 2, lines 11-13)
>
> The model used in the present invention resolves the difficulties of determining cDNA expression level measurement errors by incorporating both types of error observed in practice into a single model. The model provides advantages over existing models by describing the precision of measurements across the entire usable range of observed signal intensities. Applications of the model developed in the present invention pertain to detection limits, categorization of genes as expressed or unexpressed, comparison of gene expression under different conditions, sample size calculations, construction of confidence intervals, and transformation of expression data for use in multivariate applications such as classification or clustering. (page 3, last paragraph)

Second, one of skill in the art readily understands that determining a variance of a set of data is useful for analyzing the data, e.g., useful for showing precision. Applicant respectfully points out that the Examiner understood exactly this fact (estimating variance is estimating precision) when citing PABON. PABON notes a coefficient of variance but does not specifically state that the CV is a measurement of precision. However, the

Examiner states that "PABON teaches analysis of a coefficient of variance (CV) to show accuracy in his method."

Finally, Applicant has amended the claims to more clearly recite the relationship between determination of a variance and estimation of precision. Withdrawal of this rejection is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 2-12 were rejected under 35 U.S.C. § 112, first paragraph regarding the recitations of "y" and of "μ" in claim 2. Applicant has amended claim 2 to more clearly identify "y" as "an observed intensity measurement" and to more clearly identify "μ" as "an expression level of a biological molecule in arbitrary units." Support for the amendments are found throughout the specification as filed, as described above. Withdrawal of this rejection is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 2-12 were rejected under 35 U.S.C. § 112, second paragraph regarding the terms "error component," "background parameter," "high level," "μ," "cutoff," and the connection between the various steps in claim 2. In response, Applicant has amended claim 2 to more clearly recite the method and believes the amendments overcome these rejections.

Claims 3 and 4 were rejected under 35 U.S.C. § 112, second paragraph regarding the term "the initial set." The claims have been amended to more clearly identify "the initial set" as "an initial set A_N" that is described in step (a).

Claims 3 and 4 were rejected under 35 U.S.C. § 112, second paragraph regarding the term "until an algorithm converges." The claims have been amended to more clearly recite that convergence means when the set of genes do not change, e.g., $n_k = n_{k-1}$.

Withdrawal of this rejection is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 2-12 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Rocke et al. (1995) and Pabon et al. (2000). Applicant respectfully disagrees.

The combination of cited art does not include each and every element of the claims. Rocke et al describes a two component model for estimating analytical error of data, e.g., gas chromatography data and mass spectrometry data. Both of these sets of data include calibration data. Such data include a slope factor, β, that relates the observed measurement, y, to an observed concentration, x.

The Examiner has presented Rocke et al as providing "the same steps and equations as set forth in the instant claims." However, a closer examination of the equations shows that Rocke et al presents different equations. Rocke et al includes two equations that are similar, but not identical, to two equations from the instant claims.

Equation 1.5 of Rocke et al proposes a model for calculating an observed intensity measurement, y, using the true concentration, μ, and two analytical errors; it reads as follows:

$$y = \alpha + \beta\mu e^{\eta} + \varepsilon$$

Contrast this to Equation 1 of the instant application and claim 2, where there is no slope factor β as the gene expression data does not include a calibration curve. In addition, μ represents a relative expression level and not a true concentration, since the true concentration cannot be calculated without calibration data. Equation 1 of the instant application reads as follows:

$$y = \alpha + \mu e^{\eta} + \varepsilon .$$

Equation 3.3 of Rocke et al calculates the variance of the measured concentration x as follows:

$$\mathrm{Var}\{x\} = x^2 e^{\sigma_\eta^2}\left(e^{\sigma_\eta^2} - 1\right) + \sigma_\varepsilon^2 .$$

Contrast this to equation 3 of the instant application and claim 2; the variance of the observed intensity measurement, y, is calculated using the relative expression level in arbitrary units, μ:

$$Var\{y\} = \mu^2 e^{\sigma_\eta^2}\left(e^{\sigma_\eta^2} - 1\right) + \sigma_\varepsilon^2 .$$

Therefore, Rocke et al does not provide the same equations as the instant application. Pabon et al does not remedy this situation. The combination of art cited by the Examiner does not include each and every element of the claims.

The cited art does not teach or provide a motivation to combine the teachings. Assuming that the combination of art does contain all the claim elements (and Applicant does not concede that it does), the cited art does not teach or provide a motivation to combine the teachings. Nowhere does Rocke et al teach or suggest combining the use of the two component model for estimating analytical error of data together with data that does not include calibration data, such as data from gene expression arrays. Pabon et al, a short meeting abstract, discloses a gene microarray experiment and a coefficient of variance. Nowhere does Pabon teach combining Applicant's approach for calculating a variance (or any approach, since there is no equation) with a gene microarray experiment.

Applicant disagrees with the Examiner that one of skill in the art would have been motivated to use the statistical analysis of Rocke et al to determine a CV in order to estimate accuracy in the method of Pabon et al where the motivation would have been to use an improved method for measuring error across a full concentration range. Gene expression array data is dissimilar to analytical chemistry assay type data, e.g., gene expression data lacks calibration data.

The Examiner points to the conclusion of Rocke et al as supporting her argument. Applicant respectfully points out that the conclusion lists four examples that can be included as "a wide variety of situations;" all examples are data that include calibration data: linear calibration analyses, nonlinear calibration, censored data, and added standards data. Further, as described above, the equations found in Rocke et al include variables such as the slope factor, β, or the measured concentration x. Applicant proposes that one of skill in the art, after reading the Rocke et al, would conclude that the analysis is suitable only for data with calibration data.

One of skill in the art would have had no expectation of success. Assuming that the combination of art does contain all the claim elements (and Applicant does not

concede that it does), one of skill in the art would have had no expectation of success when combining the analysis method of Rocke et al with the gene expression data of Pabon et al. The method of Rocke et al requires the use of known quantities and a calibration curve. Nowhere does Rocke et al suggest that this method can be used with data that have no calibrating measurements (which are in any case impossible for microarray data as one would need to estimate 20,000-50,000 separate calibration curves). Application of the method of Rocke et al would have been thought not to be possible for uncalibrated measurements such as gene expression array measurements. One of skill in the art would have no expectation of success.

Therefore, the combination of art does not provide each and every element of the claims; there is no teaching or motivation to combine, and no expectation of success. A prima facie case of obviousness is not made. Withdrawal of this ground of this rejection of the claims is respectfully requested.

STATEMENT OF SUBSTANCE OF INTERVIEW

Applicant thanks the Examiner for her time during telephone interviews on January 10, 2006 and February 7, 2006. Present for the interview were Examiner Moran and Applicant's representative, Patent Agent Susan Hubl. No exhibits or demonstrations were presented or discussed. During the interview, claim 2 was discussed.

One topic discussed was amendments required to overcome the non-statutory subject matter rejection. Patent Agent Hubl indicated that claim 2 might be amended to include language regarding inputting data. Examiner Moran noted that she would require specific support in the specification for the amendments. Examiner Moran indicated that she would consider the amendment and that it was possible that the amendment would overcome the rejection.

CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicant's representative at (415) 875-2316.

Respectfully submitted,
DAVID M. ROCKE ET AL.

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By: Susan T Hubl

Susan T. Hubl, Ph.D. Patent Agent
Reg. No.: 47,668
Fenwick & West LLP
Silicon Valley Center
801 California Street
Mountain View, CA 94041
Tel.: (415) 875-2316
Fax.: (650) 938-5200

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